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Golden Face of Phosphine: Cascade Reaction to Bridgehead Methanophosphocines by Intramolecular Double Hydroarylation

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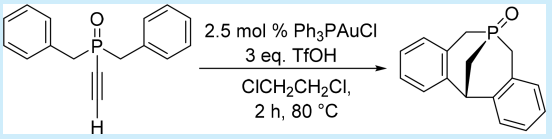
Supporting Information

ABSTRACT: Reported herein is the first example of a gold-catalyzed cyclization of bis(arylmethyl)ethynylphosphine oxides. This represents an original approach to bridgehead methanophosphocines **1**, eight-membered heterocycles. Gold catalyst in combination with triflic acid activates alkyne and induces a double hydroarylation. Mechanistic studies suggest that the reaction proceeds stepwise, forming first the 1*H*-isophosphinoline 2-oxide **5**. Reduction and protection of the corresponding phosphine oxides **1** described herein also highlight the effectiveness of our approach to this new class of electron-rich ligands.



Important toolboxes of organic transformations rely on the use of transition-metal catalysts. Among them, gold catalysis has emerged in the past recent years as an expanding field of research.[1] Compared to other common Lewis acids or transition metals, gold complexes show high preferences for unsaturated C−C bonds (e.g., alkenes, alkynes) because they are less oxophilic than other Lewis acids.[2] Therefore, gold predominantly activates C−C π-systems, making them prone to be attacked by nucleophiles including the weakest ones.[3] Established methodologies are using this unique catalytic activity of gold complexes to increase molecular complexity in mild reaction conditions. In this context, activation of alkynes by gold catalysts has emerged as a powerful method for the efficient synthesis of carbo- and heterocycles, including barely accessible ring systems.[4] As carbophilic Lewis acids, gold complexes may even activate electron-poor C−C π-bonds.[5] In a similar fashion, gold can also promote Friedel−Crafts-type additions formerly resulting on C−H hydroarylation of the alkynes.[6]

Inspired by the work of François Mathey et al. on phosphanorbornadienes, we were interested in the formation of bridgehead phosphorus derivatives through an amenable approach. The synthesis of such phosphines is sparsely described.[7] Mathey et al. have probably developed to date one of the most straightforward syntheses of monodentate 1-phosphanorbornadienes from the formal [4 + 2]-cycloaddition of 1-arylphospholes and disubstituted alkynes at 160 °C (Figure 1). When unsymmetrical alkynes were used, the regioselective formation of a specific adduct was clearly affected by the nature of the alkyne, and both isomers were generally obtained, making this method not completely generalizable.

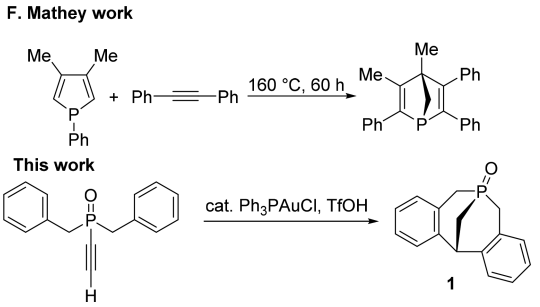


Figure 1. Bridgehead phosphine synthesis.

We were interested in an approach to conformationally restrained bridgehead phosphine derivatives. The 1-phosphabicyclo[3,3,1]-nonane core **1** (methanophosphocine core) was originally described by Issleib in the late seventies through the radical cyclization of unsaturated and pyrophoric

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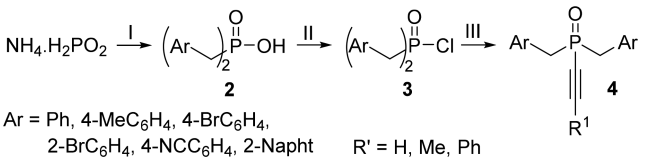
primary alkenylphosphine.[8] Interestingly, he also studied metal carbonyl complexes of such phosphines and concluded that they have virtually no π-acceptor character for the metal, making them a particularly attractive class of electron-rich phosphines. Despite these intrinsic properties, the lack of effective synthetic method impeded their development and prompted us to develop a general route to this class of compounds.

We envisioned that bis(arylmethyl)alkynylphosphine oxides might be an affordable reagent to reach this objective. Reaction with gold(I) catalysts potentially led to methanophosphocines **1** as the result of a double addition. Moreover, such intramolecular dihydroarylation of alkynes is poorly reported in the literature and is often limited to electron-rich alkynes.[9]

We began our studies by reacting ammonium hypophosphite with hexamethyldisilazane.[10] The resulting bis(trimethylsilyl) phosphonite was subjected to react with various arylmethyl halides followed by ethanolysis of the resulting phosphinic silyl ester. The expected bis(arylmethyl)phosphinic acids **2** were isolated in yields comparable of those from the literature and ranging from 34% to 58% (Table 1, products **2a–f**).[11] In a second reaction, the phosphinic chlorides **3a–f** were obtained by chlorination of phosphinic acids in almost quantitative yields. It can be noticed that 4-cyano derivative **3e** failed to be obtained in such conditions. The phosphinic chlorides **3a–d** and **3f** were consecutively engaged in the reaction with various alkynylmagnesium bromides, thus affording the bis(arylmethyl)alkynylphosphine oxides **4a–d** and **4f–i** in 50%–83% yields.[12] This straightforward method allowed us to introduce variable aryl groups and different substituents on the alkyne function (R = H, Me, Ph) in multigram scales.

Table 1. Synthesis of Bis(arylmethyl)alkynylphosphine Oxides 4a–h

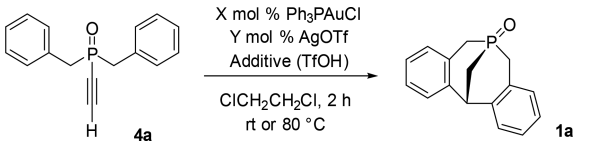


Ar	R^1	2	yield (%)[a]	3	yield (%)[b]	4	yield (%)[a]
Ph	H	**2a**	53	**3a**	99	**4a**	52
4-MeC_6H_4	H	**2b**	58	**3b**	96	**4b**	52
4-BrC_6H_4	H	**2c**	41	**3c**	100	**4c**	75
2-BrC_6H_4	H	**2d**	42	**3d**	100	**4d**	84
4-NCC_6H_4	H	**2e**	34	**3e**	0	**4e**	-
1-Naphth	H	**2f**	42	**3f**	96	**4f**	81
Ph	Me	**2a**	-	**3a**	-	**4g**	58
Ph	Ph	**2a**	-	**3a**	-	**4h**	59
Ph	cyclohexyl	**2a**	-	**3a**	-	**4i**	50

[a]Isolated yields. [b]Yields without purification.

Readily available bis(benzyl)ethynylphosphine oxide **4a** was selected as the model substrate to explore the reaction conditions for the double hydroarylation (Table 2). As expected, gold(I) catalyst (entry 1) and silver(I) triflate (entry 2) alone did not catalyze the transformation even in refluxing dichloroethane. Generally, in gold-catalyzed transformations, active gold catalysts have been prepared *in situ* by anion exchange from the relatively inert gold chloride complexe (LAuCl) through the reaction with silver triflate.[13] When silver and gold salts were used alone (entry 4), the reaction did not proceed at all. Triflic acid was next evaluated as an additive. Grisé et al. reported the benzannulation of 3-hydroxy-1,5-enynes mediated by such combination.[9b,14] Gratifyingly, methanophosphocine **1a** was formed in 5% yield within 2 h (entry 5) from the combination of gold, silver salts, and triflic acid. This reaction was then continued, and we were pleased to isolate the expected methanophosphocine oxide **1a**.

Table 2. Optimization of the Reaction Conditions



entry	catalyst [mol %]	additive[a]	T (°C)	ratio 4/5/1a (%)[b]
1	Ph_3PAuCl (2.5)	none	80	100/0/0
2	AgOTf (2.5)	none	80	100/0/0
3	none	3 equiv TfOH	80	100/0/0
4	Ph_3PAuCl (2.5), AgOTf (2.5)	none	80	100/0/0
5	Ph_3PAuCl (2.5), AgOTf (2.5)	3 equiv TfOH	80	73/22/5
6	Ph_3PAuCl (2.5), AgOTf (2.5)	3 equiv TfOH	rt	100/0/0
7	Ph_3PAuCl (2.5)	3 equiv TfOH	80	12/1/87

[a]Equivalent of triflic acid compared to reagent **4a**. [b]Determined directly by ^{31}P NMR with ^1H decoupling and with transfer of polarization (NOE).

In another set of experiments, the influence of triflic acid was evaluated. On the contrary to the results from Grisé, triflic acid alone was not able to catalyze the reaction (entry 3) even in the presence of silver triflate, excluding its role as a simple Brønsted acid catalyst.[15] Surprisingly, gold chloride combined with triflic acid afforded the desired methanophosphocine **1a** in better yield (87%, entry 7) after 2 h of reaction.

To decipher the respective roles of triflic acid and the silver salt, a kinetic monitoring of the reaction in the presence or absence of silver triflate was realized (see Supporting Information §V pages 10–15). Both reagents exhibited a determinant role in this process, and the rate of the reaction was considerably enhanced without silver salts. Moreover, such transformation was only possible in the presence of triflic acid. If precipitation of silver chloride concomitantly with the formation of the more reactive gold(I) triflate complex was generally admitted when the gold chloride complex was used, there are few but relevant examples where addition of silver may have no positive or even detrimental effects.[16] The combination of silver salts and additives was not so innocent with regard to the mechanism of the catalytic process itself. In our reactions, no precipitation of silver chloride was observed when silver triflate was used in combination with triflic acid (Table 2, entries 5 and 6). Release of hydrogen chloride mediated by the combination of the sole triflic acid as additive, gold(I) chloride complex, and temperature directly afforded the gold triflate catalyst. In parallel, a plausible explanation for reaction rate enhancement might be a double activation of alkynyl reagent **4**. The phosphoryl group was basic enough to

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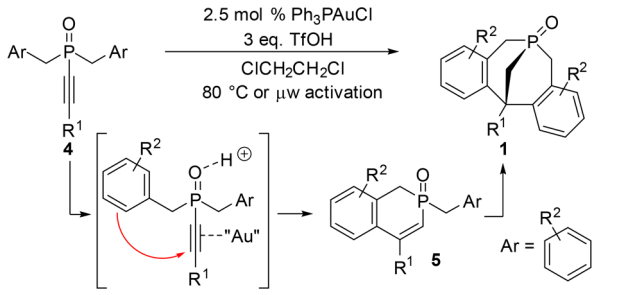
be protonated by triflic acid, making the alkyne reagent **4** and the reactive intermediate **5** even more electrophilic. Consequently, the double cyclization process was faster. To the best of our knowledge, this unusual combination of synergetic effects was still not described in gold-catalyzed reactions.

Using the optimized conditions (Table 2, entry 7), the substrate scope of this new intramolecular double hydroarylation was then examined (Table 3). Regardless of the steric

Table 3. Gold-Catalyzed Cascade Cyclization to Methanophosphocines 1a−g



entry	Ar	R^1	1	yield 5[a] (%)	yield 1 (%)
1	Ph	H	**1a**	-	98[a]
2	4-MeC_6H_4	H	**1b**	-	96[a]
3	4-BrC_6H_4	H	**1c**	-	88[b]
4	2-BrC_6H_4	H	**1d**	-	74[b]
5	1-Naphth	H	**1f**	-	86[a]
6	Ph	Me	**1g**	-	48[b]
7	Ph	Ph	**1h**	85[b]	0[b]
8	Ph	cyclohexyl	**1i**	-	-

[a]Isolated yields. [b]Required μ-wave activation.

hindrance and the electronic properties of the substituents on the aromatic ring, the expected methanophosphocines **1a−d** and **1f−g** were formed. To our delight, reaction of the phenyl derivative (entry 1) and the 4-tolyl derivative (entry 2) was almost quantitative, and the desired products were isolated in 98% and 96% yield, respectively. Similarly, even hindered bis(1-naphthyl)ethynylphosphine oxide **4f** (entry 5) was obtained in 86% yield. On the contrary, the double cyclization proved to be more difficult from 4- and 2-bromobenzyl phosphine oxides **1c** and **1d** (entries 3 and 4). Using the previous conditions, the second cyclization step appeared sluggish, affording a mixture of **1c** and **5c** in a ratio of 5/95 after 4 h of heat. The latter isophosphinoline 2-oxide **5c** was isolated and characterized confirming the sequential cyclizations to form methanophosphocines **1**. Consequently, the double cyclization was attempted under microwave irradiation, keeping the temperature at 140 °C. The expected methanophosphocines **1c−d** were isolated in 88% and 74% yield, respectively.

When 2-substitued alkynes were used, the reactions considerably slowed down, and methyl derivative **1g** (entry 6) was isolated in medium yield (48%). However, phenyl-substituted phosphine oxide **4h** (entry 7) only afforded isophosphinoline 2-oxide **5h**. We were not able to isolate any product from the reaction with 3-cyclohexylethynylphosphine oxide **4h**. A multitude of peaks in ^{31}P NMR highlighted the potential formation of rearranged products.

Combination of steric hindrance and conjugation on the alkyne moiety appeared to have a deep influence not only on the rate of the reaction but also on the reactivity of intermediate species **5**. Basically, conjugated alkynes afforded selectively isophosphinoline 2-oxides **5**. The addition of the arene group to the alkyne was fully regioselective, giving exclusively a 6-*endo*-dig cyclization by double activation of the alkyne by the soft gold catalyst and the hard phosphoryl group by triflic acid (Table 3). Consecutively, a methanophosphocine eight-membered ring was also formed through a favorable 6-*endo*-trig cyclization. For a structural confirmation of the methanophosphocine framework, a single-crystal X-ray structure analysis of **1a** was conducted (Figure 2).

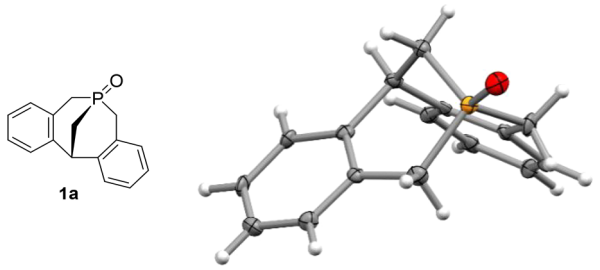
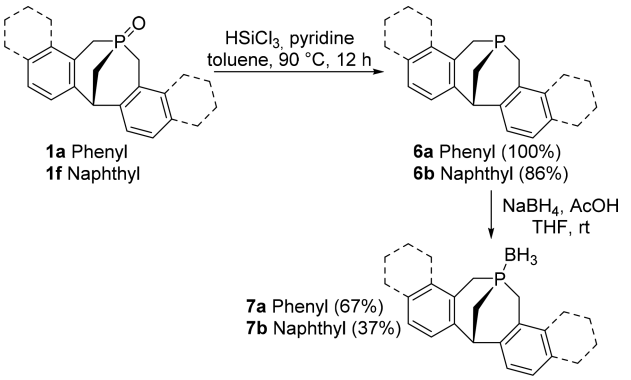


Figure 2. Ortep plot (50% thermal ellipsoids) of the solid-state structure of methanophosphocine **1a**. Phosphorus atom is shown in orange and oxygen in red.

Reduction of phosphine chalcogenides provides a general access to phosphines and still undergoes extensive developments.[17] Silane reagents are commonly used for such transformation with various modifiers, more specifically tertiary amines.[18] Reduction of methanophosphocines **1** was accomplished by direct reaction of trichlorosilane in the presence of pyridine. The heterocyclic ring proved to be tolerant to nucleophilic reductive agent, giving phenyl and naphthyl bridgehead phosphines **6a,b** in high yields (Scheme 1). As expected, these trialkylphosphines were highly sensitive to oxidation, and the prominent unshared pair of electrons on the phosphorus center readily reacted with oxygen.

Scheme 1. Reduction of Methanophosphocine Oxides 1 into Phosphines 6a,b and Phosphine-boranes 7a,b



To circumvent the oxidation reaction, synthesis of the protected phosphine-boranes **7a,b** was engaged (Scheme 1).[19] Reduction by sodium borohydride in the presence of acetic acid in THF afforded the desired products **7a,b**, albeit isolated in moderate yields after purification by chromatography on silica gel.

In summary, gold complexes proved again their unique ability to act as mild π-Lewis acids. We have found a facile

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double annulation of electron-poor alkynes into conformationally restrained bicyclic methanophosphocines **1** through a cascade sequence involving a 6-*endo*-dig and a 6-*endo*-trig cyclizations. This chemical process creates two C−C bonds and provides a simple and highly efficient entry to electron-rich phosphine oxides using an unusual combination of gold(I) precatalyst with triflic acid. Reduction of the phosphine oxides **1** proved to be efficient, leading directly to bridgehead phosphines **6** and stable borane-protected phosphines **7**. The uses as ligands or even organocatalysts of these electron-rich phosphines and phosphine boranes will be explored soon.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b03474.

Synthesis, characterizations, and spectra of the compounds **1**−**7** (PDF)

Accession Codes

CCDC 1855934 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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